actinic keratoses of the face and scalp. This table lists the two pivotal trials. Eight centers in the United States participated in each of these studies. After qualifying for the study, subjects were randomized in a 3:1 ratio to receive either Levulan or vehicle applicators, respectively.

In our review, the primary endpoint parameter was based on the percent of subjects who were completely cleared of all their targeted lesions at Week 8, based on an intent-to-treat population. At Week 8 if an observation was missing, it was considered a failure. In addition to the per-subject analysis, a per-lesion evaluation was performed. These analyses were done based on per-protocol instead of intent-to-treat.

In order for this drug product to prove efficacy, the sponsor has to demonstrate the superiority of Levulan solution to its vehicle in each of these two studies separately. I will be referring to these studies as Study 018 and 019 throughout this presentation.

Next slide, please.

Study 018, a total of 117 subjects from eight centers were enrolled into Study 018, where 88 subjects were randomized into the Levulan and 29 into the vehicle arm. No statistical differences were found between the two

treatment arms in regard to the demographics and baseline characteristics of the subjects.

And to answer your question, Dr. Lavin, that's showing the distribution of lesions or subjects for face and scalp separately. I think that was one of your questions.

DR. LAVIN: I asked within face and scalp, not overall.

MS. FARR: Next slide, please.

This table summarizes the results of the analysis for the primary endpoint variable, which was the percentage of subjects who had 100 percent of their lesions cleared. As is seen in this table, highly significant results were observed when Levulan was compared to the vehicle arm relative to the rate of complete clearance.

Next slide, please.

This table summarizes the results of the analysis for the primary endpoint variable for subjects who had 75 percent or more of their lesions cleared, and as you can see in this table, highly significant results were observed when Levulan was compared to the vehicle arm.

Next slide, please.

This is Study 019. A total of 126 subjects from eight centers were enrolled into Study 019, where 90

subjects were randomized into the Levulan and 33 into the vehicle arm. No statistical differences were found between the two treatment arms in regard to the demographics and baseline characteristics of these subjects.

Next slide.

This table summarizes the results of the analysis for the primary endpoint variables for subjects who had 100 percent of their lesions cleared for Study 019. As is shown in this table, highly significant results were observed when Levulan was compared to the vehicle arm relative to the complete clearance.

Next slide, please.

This table shows the result of the analysis for subjects who had 75 percent or more of their lesions cleared for Study 019. Again, as we can see, highly significant results were observed when the two arms were compared to each other.

Next slide, please.

Now, as I mentioned previously, the lesion analyses were based on per-protocol. Now I'm looking at the total number of lesions of the patients. This is Study 018. A total of 803 lesions were under the study. Of these, the data was available for only 784 at Week 8. This table gives the response rate for these lesions. Highly

significant results were observed when Levulan was compared to the vehicle arm.

Next slide, please. Thank you.

Now the lesion analysis for Study 019. A total of 1,086 lesions were under the study, and of those, the data was available for 1,066 at Week 8. This table gives the rate of response for these lesions, and, again, as we can see, highly significant results were observed when Levulan was compared to the vehicle arm.

Next slide, please.

Now, this is the subset analysis. The two data sets were merged, and subset analysis was done based on lesion counts by gender, age category, which was younger than 60 or 60 and older, skin type, and the location of the lesions, which was face or scalp. Highly significant results were observed in each one of these subcategories.

Next slide, please.

Conclusions. The results of the analysis of efficacy of the two studies, Study 018 and 019, demonstrate that Levulan Kerastick topical solution, 20 percent, is statistically significantly better than vehicle in the treatment of multiple actinic keratosis of the face and scalp.

Now Dr. Okun will continue this presentation.

DR. OKUN: This slide shows a flow chart reflecting the patient outcomes from pooled pivotal trials. It's a little complicated to look at. We'll just take a few minutes to go over it, because there is actually a great deal of information here.

Firstly, I should mention that the outcomes from the pivotal trials were pooled in this flow chart merely for illustrative purposes. This approach is justifiable because the two trials had identical protocols, and it's worth noting that the results from the two trials were not pooled in the review process. Each trial standing on its own achieved clinical and statistical significance.

DR. DRAKE: Excuse me. Could I ask you to bring the mike a little closer?

DR. OKUN: I apologize. I'll try and be more conscious of that.

Only two patients in the active treatment arm were discontinued due to adverse events experienced during light treatment. Five others in the active treatment arm and three in the vehicle arm were lost to follow-up.

A couple of points suggest themselves from this slide. First of all, clearly the majority of patients who were treated with Levulan experienced 100 percent complete response by Week 8. You have 180 being treated here, and

at Week 8 117 are counted as clear, 60 as not clear, with a couple dropping off, to explain how the numbers add up. Most of those who were clear at Week 8 remained clear at Week 12. Of those retreated at Week 8, which is over here, about half had 100 percent complete response by Week 12, going from here to there. And when you look in the vehicle arm, obviously, of those treated at Week 0, an extremely small number were 100 percent completely cleared by Week 8.

Next slide.

This slide shows a table recapitulating the 100 percent complete response rate of the pooled pivotal trials, looking not only at all patients, but also the subset analysis, the patients with face and with scalp lesions, both at Week 8, as over here, and at follow-up at Week 12.

Several conclusions suggest themselves from this table. Firstly, that active treatment is superior to vehicle. Retreatment at Week 8 improves overall efficacy, going from 65 percent to 69 percent, and the recurrence of scalp lesions between Week 8 and Week 12 reduces the scalp subset efficacy when you're comparing across those two time periods. Finally, across both time periods, outcomes for patients with face lesions were superior to outcomes for patients with scalp lesions. A possible reason why

patients with face lesions fare better is suggested in the following slides.

Next slide.

This slide shows the lesion response rate at Week 8 from the pooled pivotal trials, looking across different lesion grades, where Lesion Grade 1 are the thinner lesions and Lesion Grade 2 are the thicker ones. What you can see is that the lesion response rate is better comparing Levulan versus vehicle, and also somewhat better for thinner lesions compared to thicker lesions. One possible explanation for this might be that percutaneous penetration of Levulan may be superior in thinner lesions, thus making treatment more effective in that subset.

Next slide.

In comparing the distribution of lesion grades in the different sites at baseline, it's clear that the majority of face lesions are thinner, while the majority of scalp lesions are thicker. Since, as the previous slide showed, thinner lesions respond better to treatment, it may be that the higher proportion of thinner lesions on the face explains the greater efficacy for patients with face lesions.

Next slide.

In assessing safety, 232 patients, which

includes patients enrolled both in Phase II and Phase III studies, with Fitzpatrick skin types ranging from I through IV were treated with Levulan 20 percent solution and between 6 and 10.9 joules per centimeter squared blue light. There were additional patients in the Phase II studies, but there were 232 who were treated under these conditions. There were no deaths, serious or systemic adverse events attributed to treatment which emerged during the clinical trials. Transient local cutaneous adverse events occurred in most patients.

Next slide.

This slide shows the incidence of adverse events in the period between drug application and light treatment, and it shows the fraction of patients who reported any sign or symptom. Patients treated with Levulan, about 44 percent reported burning and stinging at some time point between drug application and light treatment, compared to 10 percent of control, and about 13 percent active treatments had edema. It is possible that these symptoms result from inadvertent exposure of the target lesions to ambient light in the time period between drug application and device activation, perhaps thereby initiating a low-grade photodynamic response. The alternate possibility is that the Levulan itself is

directly a dermal irritant.

Next slide.

This slide shows, in the time period during and/or 24 hours after light treatment, the fraction of patients who report burning, stinging, or edema at any time in that interval. One hundred percent of the Levulan-treated patients reported at least some degree of burning or stinging in this time period, compared to about 50 percent of the controls, and 48 percent of Levulan patients had edema on at least some of their target lesions, compared to 0 vehicle.

Next slide.

Fifty-seven percent of the patients characterized the burning and stinging as severe at least at one time point during this time interval. Dr. Piacquadio's point is well taken that for the vast majority of patients who reported severe burning or stinging at one of those time points, they did not necessarily have severe burning and stinging during the entire time period. This is just the percentage of patients who reported that at least once during that time interval. The edema and burning/stinging usually resolved within 24 hours after light treatment, and more than 90 percent of the patients eligible for retreatment at Week 8 were willing to undergo

retreatment.

Next slide.

This slide shows adverse events noted longer than 24 hours after light treatment. Specifically discussing the adverse events that developed in more than 5 percent of patients, the most common adverse event is scaling, crusting, scabbing as these lesions resolve.

I'd like to make special mention of the prevalence of -- rather, the incidence of hypo- and hyperpigmentation, which was 27 percent in Levulan and in vehicle. What this number refers to is the percentage of patients who developed hypo- or hyperpigmentation on at least one target lesion during follow-up after treatment. This analysis is a little different from the sponsor's analysis, because they were looking at the per-lesion likelihood of hypo- or hyperpigmentation, and this refers to the per-patient likelihood of developing hypo- or hyperpigmentation on at least one target lesion.

Other adverse events experienced include itching, more common in Levulan than vehicle, erosions, wheal/flare, and other non-specified skin disorders.

Next slide.

Adverse events reported by a smaller percentage of patients included pain/tenderness, ulceration, bleeding,

vesiculation, pustules, and dysesthesia, and these are all more common in Levulan-treated than in vehicle-treated patients.

Next slide.

Most local cutaneous adverse events were mild to moderate in intensity and short-lived. The few patients who developed ulcers on these sites, the ulcers healed without evidence of scarring.

Next slide.

Laboratory evaluations were, no clinically significant laboratory abnormalities following treatment. Two percent of Levulan-treated versus no vehicle-treated patients had normal baseline urine ALA levels that became marginally elevated after treatment. This information should be considered in the context that these marginally elevated post-treatment urine ALA levels were lower than the baseline urine ALA levels of three of the study participants.

Next slide.

In conclusion, the Levulan Kerastick topical solution, 20 percent, and blue light treatment effectively treats non-hyperkeratotic actinic keratoses of the face and scalp. Adverse events associated with treatment are local, cutaneous, not serious, generally mild to moderate in

intensity, and short-lived.

DR. DRAKE: Thank you.

All right. We've now reached the point of the afternoon where we're now going to open the discussion to the committee.

Dr. Wilkin, do you have any sort of instructions for us? We have the questions you've posed before us, and would you mind reviewing those so we make sure we try to give you the information that the agency needs?

DR. WILKIN: Yes.

DR. DRAKE: Excuse me. Just one second.

Henry?

DR. LIM: I have a question of clarification.

DR. DRAKE: Yes?

DR. LIM: Specifically on the device issue --

DR. DRAKE: I'm sorry, I should have asked for that. I apologize. You're absolutely right. That should come before we go to Dr. Wilkin.

Jon, will you pardon me for just a moment while I do what I'm supposed to do here?

Yes, Dr. Lim?

DR. LIM: Specifically on the device issue, I'd like to congratulate the sponsor for developing a very

interesting light source with a very reputable light source manufacturer, which is National Biologics.

I do have a question about how to monitor the output of this light source. This light source has a peak at 417. Most of the photometers that are in the regular phototherapy clinic are not going to be able to measure this, and I don't see in the picture that was provided an internal meter that comes with it. So what is the recommended maintenance, and how do we know the half-life essentially of these light bulbs?

MR. FELTEN: The phosphor that is used in the bulb is specifically designed to put out that wavelength at 417 nanometers. The company has done lifetime studies showing that the life of the bulb, if I remember correctly, goes out as long as 328 treatment cycles, which is long, long treatment cycles, and your question that will be addressed in one of our questions back to them will be about wavelength, about how to track the life of the bulb, and it will probably be based, on our recommendation, on some type of cycles of treatment, because all the treatment cycles are exactly the same, which would be 1,000 seconds. So we would just limit them by how many treatments they could recommend before the bulb should be changed.

But the phosphor is designed specifically for

that wavelength and that output. And they have looked also at the stability of these bulbs, and they're stable during these treatment cycles for at least an hour, maintaining the output level both in wavelength and in energy. So that has been tested.

DR. LIM: Thank you.

DR. DRAKE: For 1 hour, did you say?

MR. FELTEN: The testing shows that over an hour period of time, the bulb stays steady for wavelength and energy, which is --

DR. DRAKE: Over the period of an hour.

MR. FELTEN: Almost four times longer than the treatment cycle.

DR. DRAKE: Right.

MR. FELTEN: And then what they did is, they did a series of on/off cycles where the bulbs were run, the thing was rested, turned back on, out to over 400 cycles, and all of the machines that they looked at have at least 300-plus cycles before the bulb started to show deterioration. So we will limit their lifetime based on that kind of --

DR. DRAKE: On the number of cycles.

MR. FELTEN: Right.

DR. DRAKE: Got you. That's interesting.

Okay. I have Dr. Kilpatrick, and then Dr. DiGiovanna.

DR. KILPATRICK: Ms. Farr made a comment which intrigued me. She said that in the subjects randomized to treatment, all targeted lesions were treated, which implies, being legalistic, that some lesions were not treated?

MS. FARR: Well, they were supposed to choose -- patients who were entered to the study had between four to 15 lesions. These were the targeted lesions. So they were treating these lesions -- for example, a subject might have had four lesions, another subject might have had 10. So for all these subjects that they had chosen, all these targeted lesions had been treated, and success was --

DR. KILPATRICK: I understand. I understand.

MS. FARR: Go ahead.

DR. KILPATRICK: But your answer is no, there were no untreated lesions in individuals who were selected for treatment by randomization.

DR. DRAKE: Dr. Okun?

MR. FELTEN: Dr. Okun?

DR. OKUN: In fact, there were untreated lesions in the patients who were selected for randomization. For example, hyperkeratotic lesions were --

DR. KILPATRICK: Yes, of course.

DR. OKUN: Not supposed to be treated. It's possible in this protocol for patients, for instance, to have more than 15 lesions, and they would have no more than 15 of those treated.

DR. DRAKE: Okay. Dr. DiGiovanna?

DR. KILPATRICK: May I pursue this, please?

DR. DRAKE: I'm sorry, Dr. Kilpatrick.

DR. KILPATRICK: And may I be a little bit pedantic?

DR. DRAKE: Yes, sir.

DR. KILPATRICK: Donald Minland published a text called "Elementary Medical Statistics" back in the 1960s, in which he makes a big distinction between sampling units and measurement units, and sampling units are those units that are randomized -- here in this case, subjects -- measurement units in this case would be the lesions, and you, I think, very properly have focused on the subject analysis per subject, but subsequent to that we get into lesion analysis, and then analysis by different lesion grades. And while I'm being pedantic, I don't think it makes any difference, but there are other possible explanations for differences between lesion grades in terms of Phil's point about the distribution of different lesion

grades in different patients.

So I'm just being pedantic. I don't think it's a big issue. Thank you.

Thank you, Madam Chair.

DR. DRAKE: You're very welcome.

Dr. McGuire? I'm sorry. Now Dr. DiGiovanna.

DR. DiGIOVANNA: I'm not certain I'm at the right point to ask this, because I'm not certain it's a point of clarification, but I think that this is probably about as good --

DR. DRAKE: That's okay. We've started moving on anyway. Go ahead.

DR. DiGIOVANNA: This is a junctional sort of question, and you might be able to clarify this quickly. But what focused me on it was the last part of the FDA's presentation that the adverse events associated with this were not serious, mild to moderate in intensity, and short-lived. My understanding of this compound, from what I have in the literature that was given to us, is that it does cause oxidative damage to DNA. My understanding is that what we are doing here is attempting to treat premalignant lesions in a way that to a large extent partially treats those lesions.

We've learned a lot about skin carcinogenesis

over the last 5 to 10 years, enough to know that there are specific mutations that have been identified in skin cancers and in precancers, and that the accumulation of those mutations are very clearly associated with the development of malignancy, and the concern that I would have here is that if one is taking a large number of premalignant lesions and exposing those lesions to agents that damage DNA and are not totally eradicating those lesions, then the adverse event that I would be interested in is the long-term development of malignancy in the areas that have been treated.

And if I'm not correct that that should be what I'm concerned about, can you explain to me why? And if I am correct, then what sort of studies would be done to follow, to monitor for that outcome in these individuals who are at a high risk?

DR. DRAKE: I would ask Dr. Okun, and also, even though the company has completed your presentation, from time to time I may ask if you have something pertinent to add to that.

So, Dr. Okun, may you address that question first?

DR. OKUN: Well, I think answering that question requires a thoughtful response.

You know, I understand your concerns, Dr. DiGiovanna. First of all, just to clarify, in the conclusions we said that the adverse effects are short-lived, and it perhaps would be more precise to say the adverse events that were observed were short-lived. As was discussed in the protocol outline, patients were not followed for a period longer than 3 months. A period in which in humans carcinogenicity would be observed would be considerably longer than that time period. So in fact at this juncture, based on what has been submitted from the studies for this NDA, there is follow-up for no longer than the conclusion of those 3 months.

The issues that you raised that are potentially of concern would, I suppose, need to be addressed in terms of having longer-term follow-up on patients who are being treated with this modality to test the hypothesis about whether they are having a higher rate of carcinogenic progression.

Now, again, one consideration in this sort of study design is, obviously, we're dealing with a study population where there is already underlying risk of skin carcinogenesis, given the enrollment criteria by which they're enrolled. So special attention needs to be paid in terms of study design to think about how one would be able

to separate a theoretical or potential signal from the ALA as opposed to the endogenous signal from these folks because of their pre-existing solar history exposure.

DR. KILPATRICK: Martin, Table G-10 of the adverse events indicates that 3 percent of, I think, the patients had carcinoma of the skin. Again, is it possible that the photodynamic therapy was a causal agent in this?

DR. OKUN: These were cancers that were diagnosed before or during --

DR. KILPATRICK: Okay. Thank you.

DR. DRAKE: Dr. Lim, I think you might have a comment on this issue.

DR. LIM: Yes, just to try to address Dr. DiGiovanna's questions. I think one can look at it on two levels. One is that the mechanism of action of this topical ALA is through the generation of protoporphyrin, which, upon exposure to the active spectrum, which is a solar band, it would go the exitus state, the exitus state would interact with the oxygen molecule to form the singlet oxygen. The site of action primarily is in the cell membrane, so it would cause lysis of the cell. I don't think we can completely answer the question and the concern that you raised, specifically DNA damage. It primarily is on the cell membrane. That is number one.

Number two is that the other therapies for -- the 5-FU specifically, I'm not sure if you know it doesn't damage DNA either.

And then, thirdly, as was mentioned before, there is a very large cohort of patients with erythropoietic protoporphyria, which is an experiment in nature where they have tremendously elevated levels of protoporphyrin in the skin as well as in the red cell, and to a lesser extent in the plasma, and to my knowledge, there is no report that those patients as a group have a higher incidence of skin cancer. Dr. Poh-Fitzpatrick, who has followed a large group of patients, is in the audience, and I believe she can confirm that.

DR. DiGIOVANNA: Can I just respond to that?

DR. DRAKE: Yes, but I was going to ask Dr. Maureen Poh-Fitzpatrick to comment, too. So, John, go ahead, and then let Maureen have a say.

DR. DiGIOVANNA: You are correct that if you generate enough toxic oxygen species and other toxic agents, that you kill the cell, and I don't have a problem with that. You can do that with cryotherapy, and you can do that with a number of other agents. I have a problem with the inadequate treatment of the premalignant lesion, whereas you kill a percentage of the cells that already

have sustained one hit of a two-hit-leads-to-cancer hypothesis, and then the remaining cells, some have sustained an additional amount of DNA damage.

I did consider the point that you were talking about, that there are a lot of people who are walking around who have had high levels of these compounds for many years; however, they may have the sustained exposure to -- I don't know what the incidence of actinic keratosis in that population is, but it very well may be that those lesions occur at a lower level because they're totally destroyed early on.

I think the concern here is really the partial treatment of lesions. I think if you can destroy the premalignant lesions, you remove the problem. If you partially treat it with an agent that causes DNA damage, you've raised a different scenario, and you've taken someone who has a predisposition to cancer -- for example, an individual analogy would be someone who has a nevoid basal cell carcinoma syndrome, and they have a number of cells -- all of their cells have one hit already, and additional exposure to a DNA-toxic agent will increase their risk.

DR. DRAKE: But, as pointed out, I think one can make that argument for everything we currently use to

treat actinic keratoses.

DR. DiGIOVANNA: I don't think that's true, because cryotherapy doesn't necessarily cause selective DNA damage. It destroys the cells. I mean, if I'm wrong, please tell me, but I think these are --

DR. LIM: I'm not sure about that.

DR. DRAKE: I'm not sure about that, because you're clearly disturbing, perturbing the barrier function, and if these people go out and get more UVA exposure, how do you know you're not subjecting them to additional DNA damage? Because you've perturbed the natural protective barrier that might have been there before you froze them.

DR. DiGIOVANNA: Usually cryotherapy is a timely isolated event, and I don't know of liquid nitrogen being a DNA specifically damaging agent, like reactive oxygen species are.

DR. DRAKE: There are two people who still want to respond to this particular thing.

Joe, yours isn't in response to this, is it?

All right. I'm going to ask Maureen, whom I already asked, and Rob wants to respond.

So, Dr. Maureen Poh-Fitzpatrick, welcome.

DR. POH-FITZPATRICK: I'm Maureen Poh-Fitzpatrick. I'm professor emerita of dermatology at

Columbia University, and clinical professor of dermatology at the University of Tennessee.

I've had the opportunity to follow a cohort of patients with protoporphyria for 20 to 30 years, and in those patients, combined with the data from Dr. Micheline Matthews-Ross from the Harvard Medical School, in about 153 patients with this disease, some of whom are now octogenarians, there were no skin cancers tabulated from our databases and one with actinic keratosis.

Now, whether that means that these people never go out in the sun so, therefore, they're protected, that's a possibility. And the other possibility is that indeed there is some kind of low-grade protective effect from the porphyrin in the skin, although there is absolutely no data to support that at all.

So in point of fact, these people haven't gotten skin cancers and they haven't gotten actinic keratosis for some reason, and they're certainly not at high risk of having a genetic predisposition through some other gene -- of having a P53 mutation, for instance -- and then having this protoporphyrin alongside over a lifetime doing whatever concurrent damage it may do.

So these are the data that I can sort of throw out to help in the discussion.

DR. DRAKE: Thank you.

And Rob?

DR. STERN: I think if you look at the mechanisms going on here of carcinogenesis and you consider this 1,000-second hit, even if there are cells that do survive and they're DNA damaged, compared to the overall progression of carcinogenesis in actinic keratosis or sun-damaged skin, the biologic insult in terms of the likelihood of leading to cancer is likely to be trivial, on the one hand.

On the other hand, I think the point that John alluded to is, what are the effects of incomplete treatment, and what was disturbing to me was that even with the non-responders getting a second treatment 4 weeks after the initial prime endpoint, 8 weeks, on the lesions that at least in the people who get them -- elderly men are considered higher-risk lesions in terms of progression to carcinogenesis, all on the basis of clinical data, likelihood of metastasizing -- in fact the clearance rate went down even 4 weeks after the initial time, and these are in selected, pretty thin lesions.

My concern is, is this really ready for prime time with the data we have in terms of scalp lesions? I think the data on face lesions is clear in itself, but I

have real doubts about is this really safe and efficacious for scalp lesions if you have recurrences within 4 weeks that outweigh further clearances with an additional therapy.

DR. DRAKE: John, thank you. It's a good question, and where you might want to think about this is in Question 4 in terms of thinking about what studies might be done to continue to answer this very important question you've just asked. I mean, I don't disagree with you in terms of -- we must think about it, if nothing else just looking at the PUVA data over a long period of time. So it must be thought about.

Dr. McGuire?

DR. McGUIRE: I had a couple of points. One, unless I misunderstand the data, there appears to be no selectivity between normal skin and lesional skin. That is, the duration of fluorescence and the intensity of fluorescence are the same. And I assume that that means that the toxicity in non-lesional skin will be about the same as it is in the actinic keratoses. If I'm wrong about that, I'd like to hear about it.

But the piece of data that is most concerning to me is the one that Dr. Okun said was a little bit busy, and it is busy, but what it tells you is that after 8 weeks

of therapy, of the 117 individuals who cleared, 14 have recurred by 12 weeks, and one doesn't know if in another 4 weeks another 10 or 14 would have recurred, and then in another 4 weeks another 10 or 12 would have recurred.

We're dealing with a biological process with a time base of 10, 20, 30 years, and to make a prediction on the basis of a 12-month exposure to a particular modality seems to me to be -- I don't see how one could come to the conclusion that one is achieving remissions with this therapy, although that may very well be the case, but I think we need a longer window to look at these results.

Thank you.

DR. DRAKE: Dr. Kilpatrick, I had you down. Did you get your question answered? Okay.

Other questions?

(No response.)

DR. DRAKE: I had one.

Dan, I believe it's a slide you showed, the first one. You can't judge very well from pictures, but I can tell you from sitting here, it almost looked like a basal cell to me instead of an actinic keratosis, and maybe it's my glasses, I don't know, but I have a question.

Has the sponsor thought anything at all about superficial basal cells? And you can't change a

clinician's diagnostic acumen in this room. I mean, that's not possible. But have there been any studies at all where people went behind it after treatment and did biopsies to see what was left, what was the residual AK left, was there any tumor that was undetected? Has anybody followed these up with some biopsies post-treatment?

DR. MARCUS: I can respond to that in terms of the efficacy that has been published in the literature. There have been a number of papers on literally hundreds of patients treated for superficial basal cell carcinomas with ALA PDT with various light sources, and some of those studies have indeed used biopsies to assess efficacy. These studies have also used multiple treatment until the lesion had clinically completely disappeared. The biopsy rate of complete response in papers which have been submitted in the NDA, but, again, for basal cell carcinoma, state that they range from about 60 percent to 90 percent complete clinical response based on biopsy-proven efficacy.

But, again, these are published papers, and I can't vouch for the good clinical practice of the studies. However, the question you asked if there were any studies done, indeed there are. I believe this also speaks to the issue of partial treatment, but, again, it has been postulated as a possible treatment for superficial basal

cell carcinomas.

DR. DRAKE: Well, I know that the basal cell data -- I guess I didn't make my question clear. I know about the basal cell data, because Dr. Anderson and crew did that at Mass General when I was there. But have there been follow-up biopsies on the AK studies with your product? I'm sorry. That's what I was trying to ask.

DR. MARCUS: Thank you for clarifying. No, there have not been biopsies on this study.

DR. DRAKE: Okay.

Dr. Abel?

DR. ABEL: I have a question for clarification as to exclusions. Why were the patients on photosensitizing medications excluded? I mean, this certainly represents a large number of the elderly population, and most of these photosensitizing drugs have an action spectrum in the long UVA range, and maybe this extends to the visible light range, too, if someone wants to speak to that. But I think this would be a large part of the population that wouldn't be able to be treated if photosensitizing drugs are an exclusion.

DR. MARCUS: The exclusion of patients on concomitant photosensitizing medication was done purely for the sake of the purity of the clinical trial design. We

did not want to contaminate adverse events or greatly increase the size of the study by stratifying for it. We were also potentially concerned for additive effect. So, indeed, the adverse events you see are the adverse events due to Levulan and not due to Levulan plus any other photosensitizer.

DR. ABEL: That does bring up the issue of safety in this group of patients.

DR. MARCUS: As I say, we wanted to present to the agency and to understand the safety of Levulan, period, and we didn't seem to have trouble accruing patients who were not on photosensitizing drugs with their AKs.

DR. DRAKE: May I just suggest that that's another preemptive strike or suggestion for Question 4. I mean, that's something the agency might even think about. I think it's rather customary to eliminate photosensitizing drugs in the study when you're looking at a potential photosensitizer. I think that's pretty customary. But that kind of information gets picked up in subsequent studies.

Other questions of clarification before we ask Dr. Wilkin to explain the questions?

(No response.)

DR. DRAKE: Dr. Wilkin?

DR. WILKIN: Well, I would say that the committee's comments have already dealt with 75 percent or more of the questions that we've raised. The first one is relating to the lesions that are hyperkeratotic and how should we craft this into labeling: Should the label restrict the use of this combination drug/device to lesions that are not hyperkeratotic?

The second question is the relevance of the 75 percent or better complete response rate, is that helpful to clinicians and to patients? Would that be useful to craft into the labeling, or would the committee believe that just simply listing the 100 percent complete response rate measure would be sufficient?

And then there is language in the labeling that speaks to incidental photoexposure outside of the \clinician's office, and you've had a chance to look over the labeling, and do you have any comments that might amplify or modify that in a way that would make it more informative?

And then, finally, are there any additional studies that the committee believes would be helpful?

This is our list of things that we'd like, but if you come up with additional items that you'd like to share with us, we'd appreciate that.

DR. DRAKE: Thank you, Dr. Wilkin.

I think just so we have it very clear on the record, because there may have been members of the committee who have comments to make on the questions, but were holding them because they didn't feel that they were points of clarification, I would like to go through them one by one to make sure every member of the committee has an opportunity to contribute when they want to.

Let's please address Question No. 1: Should the label restrict use of Levulan to lesions that are not hyperkeratotic? And if so, how do you want to define what's the level of keratosis?

Oh, boy, a lot of hands. Fred, I'm going to call on you first, because I saw your hand first.

DR. MILLER: You know, I think that in the label it should just say that the hyperkeratotic lesions were not tested. But I think practically speaking what's going to happen is people are not going to use this preparation just spotting it on actinic keratoses as they're identified. The patients that we see have significant damage, and many times one actinic keratosis blends into the next one, and if you begin to spot it, when you're finished you're going to have every aspect of the skin completely covered.

DR. DRAKE: Ms. Cohen, I believe I saw your hand next.

MS. COHEN: No, I was just smiling.

DR. DRAKE: You were just smiling. All right.

(Laughter.)

MS. COHEN: I liked what he said, so I smiled.

DR. DRAKE: Rob Stern, I saw your hand, too, please.

DR. STERN: Well, I guess I feel perhaps differently at least -- and I heard Fred. To me, as I read these data, I think that until there are good data to the contrary, to my mind, there should be an exclusion about or a warning about the lack of proven efficacy both in the scalp and for hyperkeratotic lesions, because I think what I heard from Fred, which is exactly as I'd anticipate, unless there are particular exclusions that are prominent, it's going to be used widely and perhaps with an expectation of efficacy that we have nothing to expect.

And the third part, of course, is in terms of labeling, giving people some idea of what the limitations are in terms of how long these have been followed relative to the natural history of these lesions, and that will perhaps encourage the sponsor to do studies that give us further data that would allow us to modify the label in the

future.

DR. DRAKE: Phil?

DR. LAVIN: I would agree with you on the hyperkeratotic lesions, but the data are very compelling in favor of efficacy for the scalp. When you see 55 percent against 10 percent and 50 percent against 10 percent, whether you do the per-protocol or the intent-to-treat, those are strong, and those P values are real. So I think maybe the only thing that might potentially be dissuading is if the distribution of the type was imbalanced and all of the scalp ones were in the 1 category. That might be the only thing that could dissuade it, but it didn't look like that from any of the data that people were presenting.

DR. STERN: Perhaps I misunderstood it, but what I understood from the statistical presentation of the scalp data, as I recall the numbers, they went down from Week 8, approximately 55 percent response, to Week 12, approximately 48 or 50 percent response. There was about a 5 percent reduction in response, in spite of the fact that all of the non-responsive lesions at Week 8 were treated. So in other words, there were more lesions that reoccurred than there were lesions that responded to additional treatment.

So to me that is prima facia evidence. You

know, one has to go on the limited data, but my interpretation of that data is that if this stuff works on the scalp, it doesn't appear in very many cases to work for very long if you have more reoccurrences in 4 weeks than you have ability to clear with the second treatment, which is quite different than the face, where it went up in percentages. So statistically you're absolutely correct that if you kept on treating people every 4 weeks for every lesion that reoccurred, you would maintain that 50 percent.

DR. LAVIN: That's how I would say it was.

DR. STERN: But to me, as something that's approvable, those data are a pretty compelling argument against approving it on the basis of those small samples.

Am I wrong in how I interpreted those data?

DR. OKUN: Those are the data. That's correct.

DR. DRAKE: Other opinions on scalp? I want to take these two separate. Let's talk about scalp for a minute. Other opinions on scalp?

John?

DR. DiGIOVANNA: The other issue with respect to scalp is, it may be that the quality of or the severity or the thickness of the lesions was different, but it also may be that the skin is different, in that the scalp, even in those of us who are more sun-exposed on the scalp, does

have hair follicles, be they small, and actinic keratoses sometimes involve those hair follicles, and superficially the treatments that work from the outside in may destroy the superficial part of lesions and leave the deeper areas that involve the hair follicles.

So that may be one reason why we would see more recurrences in the scalp rather than on the face. That would not be because the quality of lesions treated were different.

DR. DRAKE: Dr. Kilpatrick, and then I want to -- well, Dr. Kilpatrick, right before you do it, I think Dan has a response to that. Would you --

DR. KILPATRICK: Well, because it may anticipate, I was wondering whether Dr. Stern would accept a compromise situation, where the label indicated that the scalp was not as effectively treated.

DR. STERN: It's not a matter of -- I just want people to be aware of the limited data we have and where it seems to work better and worse very clearly, not buried in the label, but in an explicit fashion. I certainly don't have any strong feelings about approvability or non-approvability and how to handle that. I'd leave that up to the agency. But I wanted to make my point in terms of from a clinical perspective, to me that's a very important

point, and how it's handled is fine.

DR. DRAKE: Okay. And then Ms. Cohen, and then I'm going to ask Dan.

MS. COHEN: If I understand correctly, everybody's going to have to go to a physician, so patients are not going to be seeing the label unless there is a patient insert or a patient information sheet that's handed to them in the doctor's office so they can read what it's about. I think they're entitled to have this information; and if it's only going to be exclusive to the physician, I don't think that's allowing consumers to make an intelligent decision.

DR. DRAKE: Bob, is it related to that?

DR. JORDON: It's related.

DR. DRAKE: Please, Dr. Jordon.

DR. JORDON: I think you need a patient handout of some sort anyway just to describe what kind of protection these patients have to use when they leave the office to come back for their photolight. There really needs to be a separate patient handout that's gone over with the physician when they go through this therapy, or it's going to be very, very difficult to protect these people.

MS. COHEN: You know, the patients who have

been seen are seen under the optimum circumstances, where they're going to be constantly reminded they should keep covered, et cetera, et cetera. But in the real world you can give patients instructions, but not necessarily are they going to be fulfilled. So this kind of thing really has to be bulleted so they see it and have it in their hand. I'd even have them sign something saying that they've acknowledged that they are supposed to wear protective covering during this process.

DR. DRAKE: Dan, would you please -- I think the sponsor had a comment.

DR. PIACQUADIO: Yes, I just wanted to make, I guess, one clarification point. I guess we're talking about two key issues here, one a regional therapeutic difference, face versus scalp, and then a therapeutic difference based upon the grade of these lesions, be it Grade 1, Grade 2, or Grade 3.

If we look at the data -- and I just happen to have this table with me -- there is a preponderance of these thicker Grade 2 lesions in the scalp for the aggregate study. There are 166 lesions of Grade 1 versus 180 of Grade 2 on the scalp, versus the face that had 551 Grade 1 lesions versus 415 Grade 2 lesions. So in the end I think we're looking at one common, unifying factor, that

there is a differential response to these thicker lesions. The majority of the differential anatomic response is probably due to the difference in allocation of the two lesion types.

So I think really the issue is, is there really this differential response of Grade 1 versus Grade 2, yes, and acknowledging that difference in the labeling so that consumers as well as physicians are aware.

DR. DRAKE: Thank you.

DR. STERN: I think that's misleading. There was a 53/47 split each way in the distribution of hyperkeratotic lesions by anatomic site. It was 53 percent face for non-hyperkeratotic and 47 percent hyperkeratotic, and exactly the opposite on the slide I saw from the FDA. There's a 30 percent difference in efficacy. How a 6 percent difference between the two groups in the distribution of hyperkeratosis can explain a 30 percent difference in efficacy, maybe Dr. Kilpatrick can explain that to me, but when I saw those slides, I said I don't know of any corrective or adjustment mechanism that would bring those efficacies by adjusting and stratifying according to that. It may well be that hyperkeratotic lesions in the scalp do even worse, but that doesn't wash it away. I'm sorry.

DR. DRAKE: Rob, I'm sorry, I'm looking at that slide --

DR. STERN: That was in the presentation.

DR. DRAKE: I know, but I'm looking at that slide, and it says -- these pages aren't numbered, unfortunately, but it says that this is the difference in lesion grade from different treatment sites? Is that the slide you're referring to?

DR. STERN: Yes, 53/47, wasn't it?

DR. DRAKE: It was a 57 -- face was 57 percent, scalp was 47 percent on the thinner lesions, but on the thicker lesions, the scalp was better than the face, at 53/43. If that's the slide you're referring to.

DR. STERN: I'm sorry. That's the difference, and so the difference is slightly greater, but still wouldn't make up a 30 percent difference in efficacy.

DR. DRAKE: But on this one, the scalp actually responded better than the face on the thicker lesions, if this is the same slide.

DR. STERN: I had thought that this is the distribution of lesions by anatomic site. Is that what this slide is? This is basically a 2x2 of type of lesions, location.

DR. DRAKE: I may have the wrong slide in front

of me, then.

DR. OKUN: No, Dr. Drake, you have the right slide. I guess my labeling of it was somewhat incomplete. The slide that you're referring to with those numbers, 57/43 and 47/53, that has nothing to do with response rate. That refers to the distribution of lesion grades --

DR. DRAKE: It's referring to lesion grades.

DR. OKUN: Yes.

DR. DRAKE: This is not response. Now, which slide talks about the response that Rob's referring to?

DR. OKUN: In terms of thickness, that would be the next slide in terms of looking at the response rate at Week 8, looking at the different subsets of thickness.

DR. DRAKE: Well, I guess I'm still a little confused, because I don't -- could you put the slide back up?

DR. OKUN: Actually, that would be great.

DR. DRAKE: Because I think this is an important issue, and let's discuss it with the slide, please. Because the lesion response rate is 88/78 just looking at lesion grades versus thick and thinner, but --

DR. STERN: If you look at 75 versus 48, I had said a 30 percent difference. It's a 27 percent difference in --

DR. DRAKE: But, Rob, I still don't know which slide you're talking about. So for me -- indulge your chairman. Let me see what you're talking about here.

DR. STERN: A hundred percent complete response rate, pooled pivotal trials, follow-up at Week 12, which to me is the ultimate ultimate, allowing for retreatments, and the difference in response rate, which I had remembered as 30 percent in the treated group in face --

DR. DRAKE: Rob, let's wait. Please, let's just get the slide up and then discuss it from there. It will take a minute, but I think it's going to be easier if we're all reading off the same page. That's what I'm just trying to get to. That way we can make an intelligent comment. Mainly me.

Tracy, just for future reference, these handouts are absolutely wonderful to trace and we love it, but it might help to put numbers on them so that when we do something like this, we could even -- you know, it would be nice to have them numbered down in the right-hand corner. Just a suggestion.

DR. STERN: It's right after that diagram that goes down and down and down.

DR. DRAKE: In the meantime, while they're trying to find that slide, I want to ask a question of the

committee. We're going to get all bogged down on this, and I don't want to, but with respect to hyperkeratotic lesions, I sense there's unanimity among the committee with having some labeling that clearly distinguishes between hyperkeratotic and non-hyperkeratotic lesions. Is that correct? May I have a show of hands?

(Show of hands.)

DR. DRAKE: Dr. McGuire suggests maybe even photographs would help. Nonetheless, I think for the agency's purposes, then, there is unanimity from the committee that there should be some labeling that distinguishes between hyperkeratotic and non-hyperkeratotic lesions in this study. That's one issue.

Jon?

DR. WILKIN: Is it the sense of the committee that if we just put response rates by grade, is that what you would like, or do you actually want limitation, or is this more of an informational thing?

DR. DRAKE: My sense, from what I've heard around the table -- and I guess I'd ask the committee to correct me if I'm wrong, but I think the committee wants the information out there so that people clearly understand what they're dealing with.

Is that a correct assumption?

DR. DiGIOVANNA: I think there are two issues. One issue is that the very hyperkeratotic lesions that were not studied, that it should be indicated that they were not studied.

DR. DRAKE: They were not studied, fine.

Is there any disagreement with that?

(No response.)

DR. DRAKE: Okay. Done.

DR. DiGIOVANNA: And the second issue is the thinner and the thicker lesions, and that's an informational issue.

DR. DRAKE: I think there's unanimity on that. All right. Okay. So we've got that.

Now, I'm interested in the scalp stuff.

Phil?

DR. LAVIN: Thickness should also be broken out by face or scalp, because I think the efficacy data are there, it's just a question of showing it.

DR. DRAKE: Now, is this the slide you're referring to, Rob?

DR. STERN: Yes. So how I read this, if you look at the next-to-last column, to me, because of the retreatment, the last, best information we had on these individuals was at Week 12, some of whom had been treated

once, some of whom had been treated twice, and the way I read this, if you look at the last column, for patients with face lesions, we had 75 percent complete response rate; for patients with scalp lesions, we had 48 percent. I had remembered 30 percent in my head as the difference, with the vehicles responding about the same, 10 versus 12. I had remembered 30 percent as the difference. I'm sorry, it's a 27 percent difference in efficacy.

DR. DRAKE: Shame on you.

(Laughter.)

DR. STERN: And the other point is, if you look at facial lesions from Week 8 to 12 in the treated group, it went from 68 to 75 percent. This is because some -- there are two things that went on here, as I understood it. One is that people who had unresponsive lesions or lesions that were still there at Week 8 were retreated, so the increase in 7 percent is partially due to a second treatment minus any of those that reoccurred, whereas if you look at Week 8 and 12 for scalp lesions, instead of going up with the non-responsive lesions being treated, there were more lesions that came back, according to the clinicians, than went away with the second treatment.

Obviously, the data might be there that you could say, well, how many really were additional ones going

away versus going back, but the point is, within 4 weeks in the other we're already seeing more return of lesions than we are seeing additional efficacy from retreatment of lesions that were not initially responsive. And in something where you measure success -- most of us as clinicians measure success in 6 months or a year, because that's how often we see these kinds of patients typically. To have recurrences outnumber additional successes in 4 weeks is not something that makes me happy, and 57/43 versus 47/53 -- I'm sorry, again, about that, I'm a little dyslexic -- to me doesn't explain a 27 percent difference in efficacy at Week 12.

DR. DRAKE: Okay. Phil?

DR. LAVIN: Don't be hung up about the 27 percent difference, because you aren't comparing face to scalp. You're really comparing vehicle to the treatment combination.

DR. STERN: It's only 25 percent when you put in that difference.

DR. LAVIN: Right. So it's the 68 versus the 75 and the 55 versus the 48.

I think the thing that you might want to be thinking about is what would this overall projection rate lead to at 1 year or at 6 months. In fact, I did that

calculation just now. It turns out that you're projecting losing about 50 percent of the complete responders in 24 weeks. So I don't know what frame of reference that gives you, but that's what the data from Dr. Okun's chart, his algorithm chart, would lead you to project.

So a sense of how you're doing here, I think that's the only thing that I would try to take from this. I wouldn't try to read in a comparison of face versus scalps.

DR. STERN: I was merely trying to say that adjusting for the difference of thicker lesions between face and scalp can explain these differences in efficacy.

DR. DRAKE: Okay. I'm going to, in the interest of time, take the chairman's prerogative. I don't want to argue this out right now. I think that the agency has heard that there is significant concern about this area, and it needs to be addressed properly in the labeling, and they can recirculate it. But let's not argue it out at the table.

Is that satisfactory with the committee? I think they've heard the concerns loud and clear.

Ms. Cohen?

MS. COHEN: I don't want to argue the point. I just want it to be in plain language for consumers. That's

all.

DR. DRAKE: I agree with you totally.

Dr. Wilkin and other FDA folks, are you satisfied with that? Okay.

Let's move to Question 2, then. The question here is, do we want to have 100 percent -- the question is, "To what degree does including information about efficacy as measured by the 75 percent or better complete response rate add to the information about efficacy as measured by the 100 percent complete response rate measure?"

I'll call for comments on this question. Phil?

DR. LAVIN: This is more from a perspective of robustness, and I think it is wise to have both pieces of information provided in the labeling. It gives someone a good confidence level of what the numbers are like if you don't have complete responses, and I think it is a clinically meaningful outcome to have 75 percent of all the lesions cleared.

DR. DRAKE: Does anybody disagree with that statement?

DR. DiGIOVANNA: I don't disagree with it. I just don't know how much more information it would add, since it was so difficult to communicate the meaning of complete response, since it was used in two different ways,

complete response of each lesion and complete response of an area.

DR. DRAKE: Any other comments? Fred?

DR. MILLER: I do think it's really important to get all the data in --

DR. DRAKE: Yes, I do, too.

DR. MILLER: And it's important to say that a significant percentage of these people had only three out of four lesions clear completely, and the language just has to be worked out so that indeed it is clear.

DR. DRAKE: Okay. Any disagreement with that last statement?

Dr. Wilkin, other questions from the agency on that?

(No response.)

DR. DRAKE: All right. Question 3. The question here is, does the language present in the label and patient package insert satisfactorily forewarn patients about exposure to solar or incandescent light during the period between application of ALA and administration of the light?

Dr. Bob Jordon, and then Dr. Henry Lim.

DR. JORDON: The only package insert I have was in the original material, and it's 20-some, 25 pages long,

with lots of technical stuff in it, and this is not what we're talking about here in terms of alerting patients as to what this therapy is and what kind of risks they take.

DR. DRAKE: Dr. Lim?

DR. LIM: The same point. I think we need to see what the language is going to be, but it should be there.

DR. DRAKE: And Dr. Miller?

DR. MILLER: In the information that we had, there was nothing about post-therapy protection, and they talked about 4 weeks having a decay period, but there was nothing about the post-treatment period.

And I had a question about fluorescent lighting. You know, patients are going to say, "Do I have to become reclusive in my home? How covered do I have to be?"

DR. DRAKE: "I don't have to go to work tomorrow."

(Laughter.)

DR. MILLER: In lots of areas of Pennsylvania there are kitchens with banks of fluorescent lights. They're very bright.

DR. DRAKE: Okay. Dr. Mindel?

DR. MINDEL: I was not clear -- and I don't

know whether a patient would be -- as to why, if the treatment is interrupted for any reason, it should not be restarted. And what does a patient do, then?

DR. DRAKE: That's a good question. Yes, it sort of leaves you hanging, doesn't it?

(Laughter.)

DR. DRAKE: That's a good pickup. I hadn't even -- I didn't even pick up on that.

DR. STERN: The good thing about ALA photosensitivity is, you know when it's happening, because it burns and stings. So the one thing that protects -- I personally believe what I think I'm hearing from Ms. Cohen, that you need something very explicit designed for patients to be given at the time of treatment or before they sign on the line. But the nice thing about ALA photosensitivity is, it hurts when you're doing it. It's not like a delayed reaction, when you can be out in the sun all day and then 4 hours later realize you've overdone it. So most people know when you're face is stinging and burning, it's -- not that they're not going to get edema from it, but that's usually a hint that it might be a good idea to stop doing what they're doing.

DR. DRAKE: Other comments on this question?

MS. COHEN: It says here that the stinging and

burning subsided between 1 minute and 24 hours. I mean, that's a big parameter, between 1 minute and 24 hours. So I don't know how they're going to explain that.

And also it says here that sunscreen will not protect people, and that's a very important point that should be on a consumer package, "Sunscreen is not going to protect you."

DR. DRAKE: Unless it's an absolutely opaque sunscreen. Then it would.

MS. COHEN: A veil.

DR. DRAKE: Dr. Mindel?

DR. MINDEL: Just a suggestion, too. It says in there that it shouldn't be applied around the periorbital -- the drug should not be, but I would think it would be better to say that the goggles should be on when the drug is applied in the area around the eyes, or something like that, because that's really what you want, right?

DR. DRAKE: Well, it depends on the type of goggles. Some of them have great big, wide bands, and if you're trying to treat an area on the temple, it's hard. But you've got a very valid point.

DR. MINDEL: But no matter what, if it's hidden by the goggles, it's not going to be treated, and that's

presumably --

DR. DRAKE: I agree with you, it's very important that they have the goggles there and on. And that's from our ophthalmologist guy, so we really have to pay attention.

(Laughter.)

DR. MINDEL: And I'm not going to say what I thought about these blinded versus non-blinded, either.

(Laughter.)

DR. DRAKE: Other comments on 3?

(No response.)

DR. DRAKE: All right. We're going to move to 4. We know what the sponsor and the agency have agreed to do. Now what we're being asked is what additional future studies would the committee recommend be performed, and I would like to open the discussion for that.

Dr. DiGiovanna, and Ms. Cohen after John.

MS. COHEN: Maybe he'll say it anyway.

DR. DiGIOVANNA: I think that given the frequency of actinic keratosis in skin cancer and the nature of this approach, I think that it is essential that a study be done to look at the treated lesions, in particular those lesions that have recurred in the area of treatment, to look for an increase in the incidence of

development of skin cancer, particularly squamous cell carcinoma, which often does not behave in a well-behaved fashion like basal cell carcinoma usually does, and can result in an increase in mortality. So I think that that is essential.

DR. DRAKE: Okay. Ms. Cohen?

MS. COHEN: I'm curious to know, when you apply the medication, in what form is it? Is it a cream? Is it --

DR. GOLUB: It's solution.

MS. COHEN: It's solution. Does it tend to run? Could it run?

DR. GOLUB: The way the applicator works --

THE REPORTER: We've got to get people microphones.

MS. COHEN: I beg your pardon. I know better. I'm sorry.

DR. GOLUB: The instructions with the applicator are to apply it to thoroughly wet the lesion that you're treating, without applying enough to run or drip. The Kerastick tip allows you very fine control over the amount of solution that comes out of there. So actually it will release some, and it can be absorbed back in. I mean, you can work with that Kerastick applicator.

And I think after a brief experience with it, the clinician will be able to control that.

MS. COHEN: Well, my concern is, as with Dr. Mindel, if people tend to perspire and you're doing this in a climate that's fairly warm, would it run in any way or get into the eye? Because I've read this carefully, and that worries me. It might not be a worry to you, but it worries me a little bit. Is that valid?

DR. DRAKE: The sponsor wants to respond to that.

DR. MARCUS: Yes, we can respond to that.

The issue about the eye was primarily, Ms. Cohen, because of the presence of alcohol in the solution that can burn. But our Phase III trials were done in warm, sunny climates where perspiration is very common, and there have been no instances of ocular adverse events seen as a result of running into the eye.

MS. COHEN: But you would put on your labeling, just in case by some strange reason it gets into the eye, how to clear it out.

DR. DRAKE: It's already in there.

DR. MARCUS: Yes, it's in there.

DR. DRAKE: Dr. McGuire?

DR. McGUIRE: I think the items in Question 4

are important. We have seen data that I think has been minimized. I don't think we've spent enough time on it, and I know no one wants to spend anymore time at this time of day, but I would like to see a follow-up on the cohort who were retreated at Week 8 and then relapsed. I'd like to see, in fact, the entire treatment arm. There were 56 who were retreated, and of that 56, 36 did not clear. That was with the second treatment. It seems to me that it's incumbent both on the sponsor and the agency to see what the histology of those lesions shows, as well as to find out what the histology is of the 14 who recurred after clearing at 8 weeks -- in other words, the 14 of the 117 who were clear at Week 8 and then relapsed by Week 12.

I emphasize that we're looking at a very narrow time frame here in a disease that lasts months and years, and it should be emphasized in whatever packaging you have that the data that we have is based on a 3-month study.

DR. DRAKE: I have to tell you, as a chairman's comment, I want to reinforce -- I agree. I had on my list of comments to say what Dr. McGuire just said. I think there needs to be some histology on these unresponsive or quickly recurrent lesions. So I want to really reinforce that.

Dr. Kilpatrick -- I'm sorry, Rob, you were

next. I apologize. Then Dr. Kilpatrick.

DR. STERN: Although it's probably clear from what I've said before that I think some longer-term studies are needed in terms of recurrence rates, type of lesions to recur and natural history, I think the reality is, we're going to have to use the surrogate measure of clinical actinic keratoses and not basal or squamous cell carcinoma in these areas, just because of power considerations, because of the incidence of these lesions. I mean, we can't expect the sponsor to set up a study that would have to enroll in a reasonable period of time many hundreds to thousands of patients. On the one hand, I think that would be not a reasonable burden for the sponsor.

On the other hand, I would emphasize that actinic keratoses are hard to monitor over time, both because of differences in clinical perception of them and because they in fact change over time, and that simple follow-up of 70 or 100 or 150 patients in an unblinded way is in fact, to my mind, not likely to give one robust and interpretable data, that one really has to think very carefully not only about patient safety in the design of the trial, but a design of a trial that will minimize biases, both with respect to other therapies and especially with respect to observer biases.

So this is not an easy, let's-see-how-they're-all-doing-a-year-later kind of trial, in my mind, but on the other hand, I don't think we'll be able to determine the cancer risk.

DR. DRAKE: Dr. Kilpatrick?

DR. KILPATRICK: He's just stolen my thunder, because I was trying to say, but not as effectively --

DR. DRAKE: I should have let you go first.

DR. KILPATRICK: But I'd like to add onto Dr. Stern that I'd like to -- and pick up on what Ms. Cohen was saying. We're talking about a safety study of at least 70 additional patients. I don't think that's big enough. I'd like to see a follow-up study or some type of postmarketing study of people who use this thing to see how effective the label is, what untoward effects they get if they do not follow rigorously what they're told to do in terms of exposure to sunlight, et cetera, et cetera.

Again, I'm on the same petard that Dr. Stern is. I don't know how much we can ask the sponsor to do of this, but I would like to see follow-up of the people using this after it's been marketed.

DR. DRAKE: Dr. Lim, and Dr. Miller.

DR. LIM: It's a question of clarification also. "Thirty of whom have Fitzpatrick skin type IV to

VI," what is the purpose of doing it? Because especially in skin type V and VI, it's going to be very, very low to have actinic keratosis in those patients. It would be very difficult to find those patients.

DR. OKUN: Your point is very well taken. I would anticipate that the majority of those 30 would probably have Fitzpatrick skin type IV. And to answer the question about why we're interested in that, our concern, I think, stems from whether there would be differences in terms of postinflammatory hypo- or hyperpigmentation as a function of increasing baseline skin pigmentation among the higher Fitzpatrick skin types.

DR. DRAKE: Dr. Miller?

DR. MILLER: I want to follow up on Dr. Stern's comments. I think that there's a lot of subjectivity looking at lesions that are healed or clear, and I think it would be good to have biopsies on lesions that are clinically clear on a group of those patients, so that are they truly totally gone after the therapy, and maybe this would explain some of this recurrence, you know, were they not gone to begin with.

DR. DRAKE: Actually, that's a very good point.

I think what you're hearing, Dr. Wilkin, from this whole group is that there's -- actinic keratoses are

so fickle, because a certain percentage of them spontaneously remit, a certain percentage of them evolve into squamous cells.

And just as an aside, the most recent argument or discussion at the American Academy of Dermatologists was whether these are premalignant. That terminology is being challenged vigorously. Most people believe these are in squamous cell in situs, they're squamous cell in situs, they're not premalignant, they're actual in situ malignancies. And I can tell you, I think there's a drift toward that, because that's the leading opinion of dermatopathologists and a lot of our skin cancer specialists, skin oncologists.

So I think what you're hearing is a level of discomfort with just saying they're gone, without some histologic proof or some follow-up of the biologic activity of these lesions to see what they do after they've been treated.

Is that a fair way to state that? Okay.

Elizabeth? Dr. Abel?

DR. ABEL: I would also like to see follow-up studies on patients who are on photosensitizing drugs, and perhaps to clarify that statement on clearing, is there clearing to a macular state with no obvious scale? To sort

of refine that definition of clinical clearing.

DR. DRAKE: Dr. Lim?

DR. LIM: I just have a question to follow up on Dr. Abel's question. In terms of the photosensitizing medication, I think that would add another layer of complexity. It would be very hard to analyze the data, number one, and, number two, in patients with PUVA, we know we put patients on PUVA as long as they're not on highly phototoxic medications, and we have had no problem with those.

I'm not sure, one, what additional information you would get, and, number two, I think it would make the data analysis so much more difficult to know what is going to be effective.

DR. ABEL: I think that there has to be some limited study on these patients for people to feel comfortable about treating them. If there is no data at all --

DR. LIM: Right. But on the other hand, we know the light source is at 417, and most of the photosensitizer is going to be at the UVA range. This is beyond UVA. So I don't think it's going to be affected.

DR. ABEL: Then it's not an issue, you're saying.

DR. LIM: I don't think it will be a significant issue.

DR. STERN: I would agree with Henry that for most marketed drugs, this treatment is not an issue in terms of photosensitizers. I'd have to look at sparfloxacin and see how far it goes up, but the number of drugs I'd be concerned about is tiny.

DR. DRAKE: Dr. Wilkin?

DR. WILKIN: I think that's close to what our opinion was. We believe that if there was no photochemistry, there wouldn't be photobiology, and that --

DR. DRAKE: That's right. Details.

(Laughter.)

DR. WILKIN: And that in essence what we could do is, we could actually speak to the drugs that might be of concern.

DR. DRAKE: I think that's fine.

Now, Dr. Wilkin and the other folks from the FDA, have we answered these questions satisfactorily? Have you gotten enough information?

Don't people start packing up and leaving just yet. I'm not done.

DR. WILKIN: We have a lot of great information.

(Laughter.)

DR. DRAKE: Are there any questions that we've left unanswered? Tracy just wants to make sure you have an adequate answer for restrictions.

I think what I did, Tracy, is put that back into the -- I think they've heard all the comments around the table, and I think we'll let the folks at the FDA digest all this and come up with something reasonable. They've heard a variety of opinions.

Dr. Wilkin?

DR. WILKIN: Yes, I think what we heard from the committee was not really something along the line of restriction, but full disclosure in labeling --

DR. DRAKE: Full disclosure is what we heard.

DR. WILKIN: That we really describe the differences in scalp and with the hyperkeratotic lesions, and the two aspects that Dr. DiGiovanna mentioned, one, the hyperkeratotic lesions that were not studied, and then the different grades and the response at different grades. And also the follow-up, that second treatment visit, we may want to craft a little more of that information for scalp into labeling as well. I think that's what our encouragement was to do.

DR. DRAKE: Anything else that the FDA needs

from anybody? Are you okay with all this?

DR. WILKIN: Well, I would thank the committee and the invited experts from yesterday afternoon and the sponsors from yesterday morning and this afternoon. I think we had an amazing amount of really good information presented, and we had great feedback from the committee in answering questions on difficult topics, and three very different and difficult topics. Helpful for us.

DR. DRAKE: Okay. And I want to say two or three things.

First of all, I want to thank the sponsor for your time and effort and your research and the funds that you spend and the personnel you expend and the decisions you've made to help support research into products that will help our patients with skin disease. We're very appreciative. We understand it takes a lot of work, a lot of effort, and your life is sort of in our hands here for a few moments, and that must be very stressful. But when you give us clear data and clear presentations, it's easier for us to help advise the FDA.

We just want you to know that we're grateful to you for your support of research into new therapeutics for skin disease. Our patients are all grateful.

And I want to thank the consultants for coming

today. It's very nice.

I also want to thank the FDA. First of all, I want to thank Jonathan for your leadership. You know, there have been some new strides made. That session we had on hand dermatitis was wonderful. I mean, it just seems to me there are so many things that you're doing to make us able to do our job better. We're very grateful, from the community of dermatology. So I'd like to thank you and all your staff for your excellent presentations and organization.

And Tracy, our executive secretary, this has been a -- she didn't even eat lunch.

You get to eat supper tonight.

She hasn't eaten in 2 days. So we want to thank her for all her hard work. She has just gone full bore.

And thanks to the audiovisual people.

And most of all, I want to thank the committee. You guys are great. This is such a solid committee. I mean, you just really come forward with good, solid comments. There are no petty biases. I'm very, very proud of you, and I'm very proud to work with you. Thank you.

And, Henry, you have a question?

DR. LIM: One comment. During the last

meeting, we didn't realize it was Joe's last meeting as a chair. I would like to, for those of us who had been in the committee for a year --

DR. DRAKE: Absolutely.

DR. LIM: To just express our appreciation for Joe's leadership.

(Applause.)

DR. DRAKE: And don't assume it's past tense. He still was doing a lot of help in here today. Over the last 2 days, I had a lot of sweet nothings in my ear.

(Laughter.)

DR. DRAKE: Anyway, thank you, and you're going to all make your planes. Thanks for the hard work. Bye.

(Whereupon, at 3:56 p.m., the meeting was adjourned.)